Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans

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Cooke, William H., Kathy L. Ryan, and Victor A. Convertino. Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. *J Appl Physiol* 96: 1249–1261, 2004; 10.1152/japplphysiol.01155.2003.— Hemorrhage is a leading cause of death in both civilian and battlefield trauma. Survival rates increase when victims requiring immediate intervention are correctly identified in a mass-casualty situation, but methods of prioritizing casualties based on current triage algorithms are severely limited. Development of effective procedures to predict the magnitude of hemorrhage and the likelihood for progression to hemorrhagic shock must necessarily be based on carefully controlled human experimentation, but controlled study of severe hemorrhage in humans is not possible. It may be possible to simulate hemorrhage, as many of the physiological compensations to acute hemorrhage can be mimicked in the laboratory by applying negative pressure to the lower extremities. Lower body negative pressure (LBNP) sequesters blood from the thorax into dependent regions of the pelvis and legs, effectively decreasing central blood volume in a similar fashion as acute hemorrhage. In this review, we compare physiological responses to hemorrhage and LBNP with particular emphasis on cardiovascular compensations that both share in common. Through evaluation of animal and human data, we present evidence that supports the hypothesis that LBNP, and resulting volume sequestration, is an effective technique to study physiological responses and mechanisms associated with acute hemorrhage in humans. Such experiments could lead to clinical algorithms that identify bleeding victims who will likely progress to hemorrhagic shock and require lifesaving intervention(s).

combat casualty care; simulated hemorrhage; central hypovolemia; autonomic cardiovascular regulation

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IN TRAUMA AND COMBAT CASUALTY care medicine, a need exists for a physiological algorithm that will predict survival outcome (82). Despite ongoing study, altered mentation and low-blood pressure (systolic < 90 mmHg) are still considered to be the best indicators of the need for life-saving interventions (3, 42, 44, 101), even though the unreliability of arterial blood pressure as an indicator of blood loss was recognized as early as the World War II era (49, 100). The development of an effective algorithm would facilitate triage as well as define resuscitation strategies for hemorrhagic shock (23, 82). Despite the need for the development of such a diagnostic tool, the ability to experimentally study the hemodynamic effects of hemorrhage is currently limited either to animal studies or to human studies in which blood loss is induced by voluntary blood donation. Application of information derived from such studies to a triage algorithm meant for humans is limited by species differences and the possible presence of anesthesia in the former case (30). In the latter case of human blood donation, the removal of only small percentages of total blood volume is easily compensated for in most cases and does not provide predictions as to the point at which blood pressure decompensation will occur with greater volumes of blood loss.

Application of negative pressure to the lower body redistributes fluid from the upper body to the lower extremities, allowing for the study of hemodynamic responses to central hypovolemia (23, 90, 125). Since the first description of this research tool (106), lower body negative pressure (LBNP) has been used by aerospace investigators to study such physiological phenomena as postspaceflight orthostatic intolerance and exposure to vertical acceleration in high-performance aircraft (23, 125). In a previous article, Convertino (23) investigated the utility and reproducibility of LBNP as a technique to study cardiovascular adjustments to such stressors and suggested that LBNP might also be a useful surrogate to study hemodynamic effects associated with severe hemorrhage in humans for military applications, specifically combat casualty care research. It should be emphasized that LBNP has been used since its inception as a model to study hypovolemia (e.g., Refs. 10, 13, 32–34, 40, 54, 58, 65, 66, 74, 79, 81, 83, 87, 90, 91, 93, 109, 115). However, there is renewed interest within both the Army Medical Department and the National Institutes of Health (17) in studying hemorrhage in a human model, as hemorrhage is the primary cause of death on the battlefield (9) and a leading cause of death in civilian trauma (8, 94, 99). Although physiological responses to both experimental hemorrhage (67, 95) and clinical trauma (e.g., Refs. 39, 82) have recently been reviewed, the use of LBNP as a model to study hemodynamic responses to hemorrhage has not been adequately addressed.

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The purpose of this review is to integrate data from both experimental animal and human studies to examine the utility of LBNP as a model to study acute hemorrhage leading, ultimately, to hemorrhagic shock. Classic and recent papers describing cardiovascular responses to hemorrhage form a base to search the literature for LBNP studies that focus on similar responses. Our first goal is to equate magnitudes of blood loss to magnitudes of chamber decompression. Second, physiological responses to hemorrhage and LBNP, including relative bradycardia, regional, and neurohumoral responses, will be compared. Third, mechanisms underlying hemorrhagic shock and cardiovascular collapse during hemorrhage and LBNP will be evaluated with specific focus on sympathetic neural activity. Based on the assumption that cardiovascular responses are similar, we will review the logic and evidence concerning the hypothesis that LBNP is an effective model to study acute hemorrhage in humans.

RESPONSES TO HEMORRHAGE AND LBNP

Under both conditions of hemorrhage and LBNP, the stimuli for cardiovascular compensation are similar: both decrease venous return and preload, resulting in decreased stroke volume and cardiac output. Schadt and Ludbrook (95) divide responses to experimental hemorrhage in conscious mammals into two phases. The first phase is characterized by a sympathoexcitatory response, resulting in maintenance of arterial blood pressure at baseline levels. In the second phase, blood pressure decreases due to a pronounced sympathoinhibition, resulting in vasodilation and bradycardia. Jacobsen et al. (60) outlined a third stage, in which severe hemorrhage is associated with tachycardia and failure to maintain microvascular blood flow, leading to tissue ischemia, cellular dysfunction, and death (59, 122). Similar stages describing responses to LBNP have been delineated (35). For more effective triage, it is necessary to develop procedures and algorithms to predict progression to stage 2 hemorrhage, before it occurs, to avoid stage 3. LBNP may be useful in this regard. Cardiovascular responses to LBNP are reproducible in the same subjects studied more than once in the same physiological state, and the procedure is safe because symptoms of progression to cardio-

Table 1. *Classification of hemorrhage severity in humans and magnitudes of lower body negative pressure*

LBNP	Hemorrhage
10–20 mmHg	Mild
400–550 ml fluid displaced	400–550 ml
	$\cong$10% of total blood volume
20–40 mmHg	Moderate
500–1,000 ml fluid displaced	550–1,000 ml
	$\cong$10–20% of total blood volume
$\geq$40 mmHg	Severe
$\geq$1,000 ml fluid displaced	>1,000 ml
	>20% of total blood volume

Hemorrhage data are from humans and represent approximations and ranges from the literature. Definitions of mild, moderate, or severe hemorrhage correspond to usage in the text. LBNP, lower body negative pressure.

vascular collapse can be immediately resolved by terminating the decompression. Issues of safety and reproducibility have been reviewed in detail elsewhere (23). An example of LBNP application to a human volunteer is shown in Fig. 1.

Volume-Pressure Relationships

Definitions. Throughout the literature, cardiovascular responses to hemorrhage are described as functions of either absolute blood loss, relative blood loss (i.e., ml/kg), or percentages of total blood volume. For this reason, it is difficult to directly compare the magnitude of hemorrhage with the magnitude of LBNP. Absolute equivalence between the two is also difficult to ascertain due to intersubject differences in physiological responses to LBNP. Underlying issues, such as comparisons of LBNP responses in different subject populations and experimental conditions, have recently been reviewed (23). At present, the best estimates reveal ranges of "blood loss" as functions of magnitudes of LBNP. In an attempt to establish relative physiological responses to differing levels of hemorrhage (mild, moderate, and severe) and LBNP, and for the purpose of normalizing, to a certain extent, different methods of quantifying hemorrhage, we have constructed Table 1 from literature reviewed in the following sections. When possible, in addition to describing mild, moderate, or severe hemorrhage, we have also included either absolute, relative, or percentage values, as described in the original work.

Hemorrhage. Acute hemorrhage decreases cardiac output, stroke volume, left ventricular work, mean arterial pressure, and central venous pressure (103) and, therefore, constitutes a challenge to cardiovascular homeostasis. Reduction of ~15% of the total blood volume ($\cong$750 ml) decreases cardiac output by 30% (11). During mild-to-moderate hemorrhage, arterial pressure is maintained through sympathoexcitation that increases peripheral vascular resistance and heart rate, but cardiac output falls progressively. As depicted in Fig. 2, continuous bleeding in pigs (Fig. 2A) and progressive LBNP in humans (Fig. 2B) elicit similar reductions of cardiac output and compensatory increases of heart rate.

In animals, abrupt reductions of arterial pressure occur after a threshold for blood loss has been reached. Mean arterial pressure is well maintained during slow (0.7 ml·kg^{-1}·min^{-1}) hemorrhage in sheep but falls precipitously when total blood loss equals ~24% of total blood volume (50). An early study by Henry et al. (56) documented a tight linear relationship
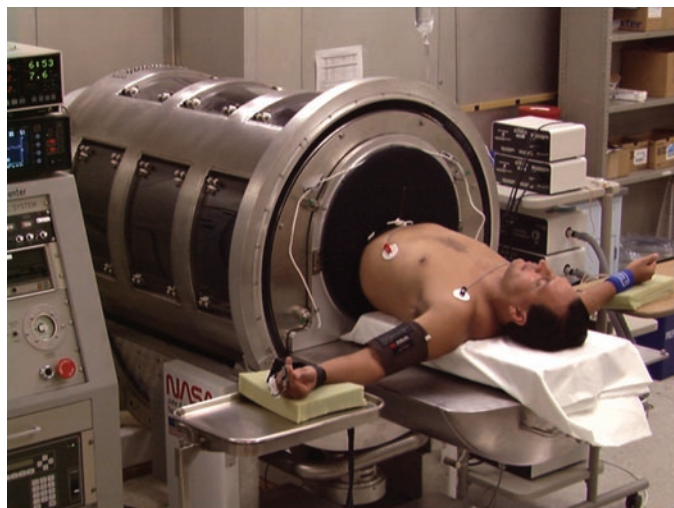

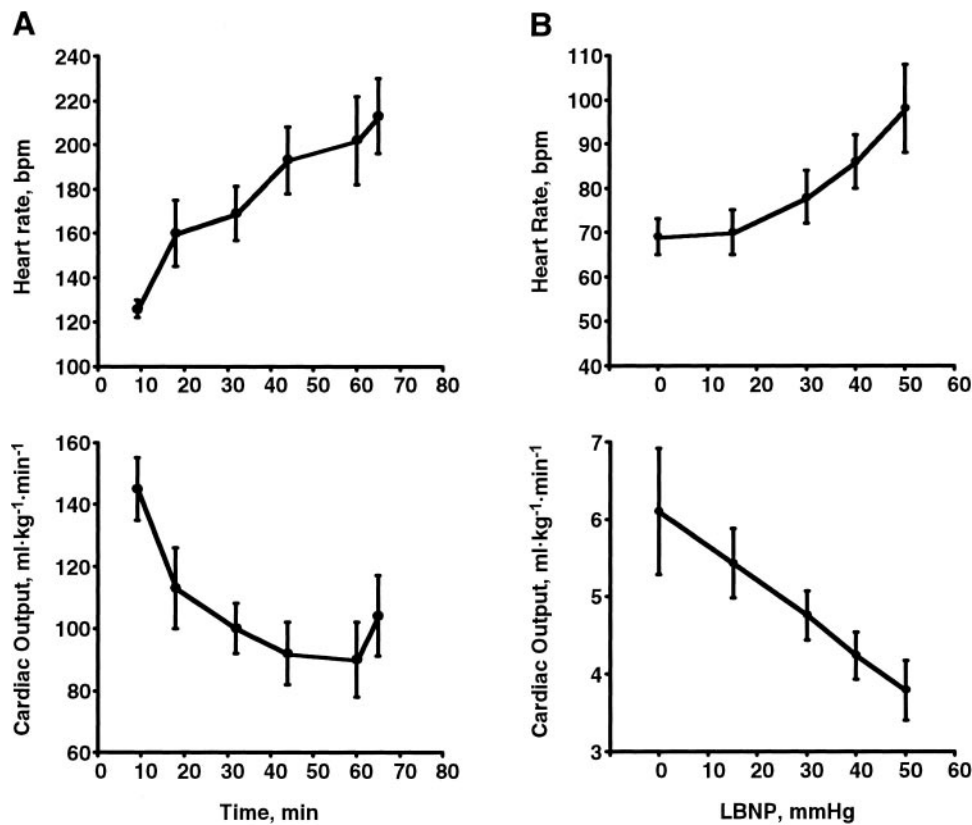Fig. 1. Subject placed in the lower body negative pressure (LBNP) device.

Fig. 2. Comparison of elevated heart rate and reduced cardiac output during 65 min of hemorrhage in 10 pigs (*A*) and graded LBNP in 10 human subjects (*B*). Circles and lines represent mean ± SE values. bpm, Beats/min. [Data modified from Hannon (53) and Convertino (23).]

between changes in blood volume between +30 and −30% of total volume, and pulmonary arterial, left ventricular diastolic, and central venous pressures in dogs. Their data reveal that left ventricular diastolic and central venous pressures decrease by ~1 cmH$_2$O for every 10% effective reduction in blood volume (56). In agreement with their work in animals (56), Gauer and coworkers (45) documented a tight linear relationship between blood volume and central venous pressure in humans.

LBNP. Based on cardiovascular changes induced by progressive LBNP, hemorrhage, and plasma volume reduction, LBNP on the order of 10 (110) or 20 mmHg (54) seems to be equivalent to hemorrhage of ~400–550 ml. Other studies have suggested that simulated blood volume reductions with progressively higher levels of LBNP are roughly linear. For example, in agreement with studies showing consistent symptoms of cardiovascular collapse with removal of ~1,000 ml of blood (84, 100), Murray et al. (73) found that all subjects studied experienced symptoms of cardiovascular collapse when progressive LBNP (from 10 to 40 mmHg) was applied after removal of 500 ml of blood. These data were interpreted to imply that, during the LBNP protocol, at least 500 ml of blood were pooled in the lower body. In a later study, Wolthuis et al. (126) concluded that 30- to 50-mmHg LBNP corresponds to blood pooling in the lower body on the order of 500–1,000 ml. Muscrave et al. (76) similarly estimated that 40-mmHg LBNP pulls from 600 to 1,000 ml of blood into the lower extremities. An apparent linear association between LBNP magnitude and lower body blood pooling is mirrored by a similar association between LBNP and central venous pressure.

Reductions of central venous pressure are directly related to the magnitude of LBNP and reflect reduced venous return and preload. Application of LBNP between 10 and 60 mmHg reduces central venous pressure by 3–7 mmHg (125), which is in good agreement with equations derived from animal studies predicting reductions of central venous pressure as a function of reductions of blood volumes (56). Norsk et al. (77) and Hirsch et al. (57) demonstrated that central venous pressure decreases by ~2 mmHg for every −10-mmHg chamber pressure, up to −30 mmHg. Rea et al. (87) documented comparable reductions of central venous pressure (~2 mmHg) after acute removal of 450 ml of blood. This estimate is in good agreement with data presented in Fig. 3*A*, which show a reduction in central venous pressure of ~2 mmHg after plasma volume was reduced by 550 ml with furosemide. As shown in Fig. 3*A*, central venous pressure was reduced by this same amount in normovolemic subjects with application of −10-mmHg chamber pressure (110). Similar associations between LBNP and stroke volume are shown in Fig. 3*B*, where application of 10-mmHg LBNP or reduction of plasma volume by ~550 ml decreased stroke volumes by ~20 ml. Also apparent from Fig. 3, *A* and *B*, is the maintenance of linear reductions in central venous pressure and stroke volume, when LBNP is applied after plasma volume reductions. Application of only 10-mmHg LBNP in conjunction with hypovolemia decreased central venous pressure by ~4 mmHg and stroke volume by ~30 ml, compared with the normovolemic baseline condition.

In eight subjects, central venous pressures decreased from ~7.5 to 5.1, 3.4, and 2.0 mmHg during chamber decompressions of 0, −10, −20, and −30 mmHg, respectively (77). Van Hoeyweghen et al. (115) also documented reductions of ~2 mmHg for every −10-mmHg chamber pressure, up to approximately −30 mmHg, at which time central venous pressures
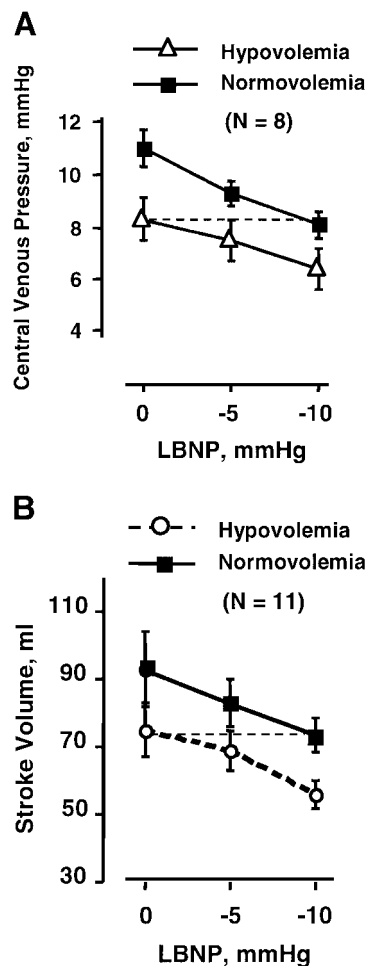
Fig. 3. *A*: comparison of relationships between LBNP and central venous pressure during normovolemia (■) and ~550 ml hypovolemia (△) and −10-mmHg LBNP. [Data modified from Thompson et al. (110).] *B*: comparison of relationships between LBNP and stroke volume during normovolemia (■) and ~540 ml hypovolemia induced by confinement to head-down tilt bed rest (○) in 11 human subjects. Symbols and lines represent mean ± SE values. Dashed horizontal lines represent comparison between 540 ml hypovalemia and −10 mmHg LBNP. [Data modified from Convertino et al. (24a).]

approached zero. Further increases of negative pressure appeared to not further reduce central venous pressure, with values simply tightening around zero at −50 mmHg (115), although negative values for central venous pressure during high-level LBNP (40–60 mmHg) are not uncommon (125). These data suggest that central venous pressure falls as a linear function of ~2 mmHg for every −10-mmHg chamber pressure, up to −30 mmHg, beyond which values are zero or negative until the onset of cardiovascular collapse.

COMPARISON OF PHYSIOLOGICAL RESPONSES

As may be appreciated from the summary data presented in Table 1, quantitatively accurate magnitudes of blood loss and associated volume sequestration during LBNP are variable. For this reason, LBNP is useful in estimating ranges of central hypovolemia associated with hemorrhage (i.e., mild, moderate, or severe), but using LBNP decompression levels as a surrogate for actual blood loss is not appropriate. The relationship between LBNP and the volume sequestered in the lower body

is a function of lower body size, lower body compliance, and lower body vascular compliance. Resulting cardiovascular responses are functions of residual central volume and numerous physiological compensations. Responses to LBNP are affected (in part) by age, body size, physical conditioning, hydration, and gender (23). In addition, physiological responses can vary among subjects who appear to be similar, and these differences may underlie susceptibility for cardiovascular collapse (23).

Specific data extracted from the literature and the subsequent descriptive responses discussed in the following sections suggest that a closer association between hemorrhage and LBNP may be achieved on the basis of physiological responses. With this construct, changes in heart rate, arterial pressure, plasma catecholamines, etc., do not relate specifically to absolute magnitudes of blood loss, but rather reflect individual responses to central hypovolemia based on adequacy and effectiveness of compensatory mechanisms. The use of physiological responses to LBNP rather than exact magnitudes of chamber decompression to simulated hemorrhage may allow for classification into stages, accurate tracking to impending hypotension, and separation of subjects who may be susceptible or not susceptible to cardiovascular collapse.

Relative Bradycardias

Hemorrhage. Although tachycardia has historically been thought to be a reliable marker of hemorrhagic shock (97, 118), relative bradycardia (heart rate < 100 beats/min; systolic pressure < 100 mmHg) occurs in ~30–35% of patients with severe traumatic hypotension and does not seem to affect survival rates compared with hypotensive trauma patients who respond with tachycardia (29, 111). Interestingly, hemorrhagic shock may be reversible in patients who respond with relative bradycardia but not tachycardia (59). Demetriades et al. (29) demonstrated that mortality due to hypotensive trauma was more predictable in tachycardic than bradycardic patients, and prognosis for bradycardic patients was better.

Bradycardic responses are likely vagally mediated, as hemorrhagic shock increases plasma pancreatic polypeptide hormone (92) and administration of atropine increases heart rate during intraperitoneal bleeding with hypotension (61). Paradoxical reductions of heart rate associated with reduced ventricular filling via the Bezold-Jarisch reflex result from increased vagal cardiac control and inhibition of sympathetic efferents. The resulting withdrawal of sympathetic nerve activity elicits vascular dilation and decreased peripheral resistance with a resultant hypotension (80). By the time bleeding patients present with tachycardia, they may be in severe trouble. A heart rate of ~120–160 beats/min during hemorrhage is associated with extreme bleeding, and these patients may not recover (59).

LBNP. In accordance with stage 2 hemorrhage, as outlined by Schadt and Ludbrook (95), LBNP studies document declining heart rates toward resting levels as the LBNP termination point is approached (6, 23, 27, 35, 75), suggesting significant vagal activation before cardiovascular collapse. For example, after an initial rise in heart rate at 55-mmHg LBNP, heart rate decreased from 90 to 57 beats/min with concomitant increases of pancreatic polypeptide hormone and decreases of mean arterial pressure from 94 to 41 mmHg (91).
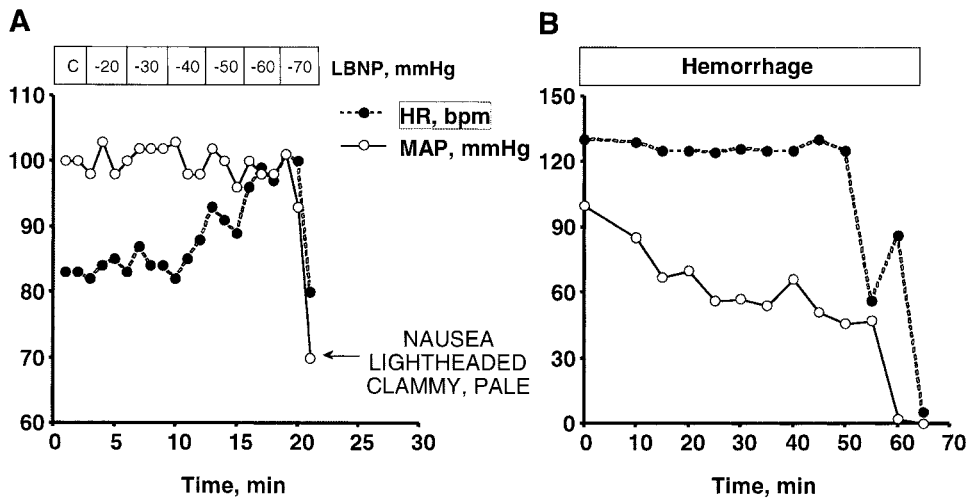
Fig. 4. Comparison of the onset of cardiovascular collapse indicated by severe hypotension and bradycardic responses measured during graded LBNP in a human subject (*A*) and during 65 min of emergency room care for hemorrhage in a gun-shot victim (*B*). C, control. [Data modified from Convertino (21) and Secher et al. (98).]

Similarities between responses to LBNP and hemorrhage are shown in Fig. 4. In Fig. 4*A*, stage 1 sympathoexcitation is suggested by increasing heart rates at approximately −40-mmHg chamber pressure, followed by stage 2 sympathoinhibition and dramatic reductions of heart rate and arterial pressure at the onset of preshock symptoms (21). Figure 4*B* depicts responses of a gun-shot victim (98). Similar sympathoexcitation is apparent, as heart rate is maintained above 120 beats/min until cardiovascular collapse after ∼50 min of bleeding (volume of bleeding undisclosed). In this example, tachycardia on the order of 120 beats/min was ineffective in maintaining arterial pressure, and this patient died.

Regional Responses

Hemorrhage. Is arterial pressure maintained during hemorrhage through systemic sympathetic activation, or does blood loss differentially affect autoregulation of various vascular beds? In monkeys, 30–50% withdrawal of total blood volume decreases fractional cardiac output to skin, kidney, and skeletal muscle and increases fractional cardiac output to heart, brain, and liver (41). Renal blood flow is well maintained in sheep during hemorrhage until systemic hypotension, at which time renal blood flow decreases and cardiac output is redistributed elsewhere (50). Renal blood flow rises during moderate hemorrhage but decreases during severe hemorrhage in dogs (117), and removal of 20% total blood volume decreases renal blood flow in conscious pigs by 30% (104). Renal sympathetic nerve activity seems to progressively increase during moderate hemorrhage but decreases abruptly during severe hemorrhage in conjunction with reductions of arterial pressure (16). Mean arterial pressure is preserved in dogs during slow (0.5 ml·kg^{-1}·min^{-1}) continuous hemorrhage until blood loss equals ∼20 ml/kg, at which time renal nerve activity increases twofold (71). Renal nerve activity returns to control levels during hypotensive hemorrhage after ∼39 ml/kg of blood have been removed (71), which may be interpreted as sympathetic withdrawal.

Price et al. (84) documented, in human subjects, the importance of the splanchnic circulation as a reservoir that may be depleted by up to 40% while central blood volume decreases by only 10% with removal of 1,000 ml of blood. Removal of ∼20% total blood volume (900–1,190 ml) increases peripheral vascular resistance by 25% and decreases renal blood flow by 22%, although the fraction of cardiac output to kidneys actually increases (107). The cerebral circulation may also be regulated independently during blood loss. Blood donation of 470 ml decreases both tissue oxygenation to the calf muscle and cerebral cortex in proportion to the magnitude of blood loss, but the greatest decrease was reported in the calf, suggesting effective cerebral autoregulation during hemorrhage (114). These results argue against the notion that hypotensive hemorrhage causes uniform regional blood loss and uniform systemic sympathetic activation.

LBNP. In agreement with studies in animals, fluid distribution and, therefore, vascular control are not uniform throughout the body during LBNP. Hirsch et al. (57) used prolonged (1-h) LBNP to study regional vascular responses. LBNP of 10 mmHg decreased central venous pressure, along with forearm and splanchnic blood flow, but did not affect arterial pressure. Higher levels of LBNP (20–40 mmHg) further reduced central venous pressure and splanchnic blood flow while forearm blood flow returned to baseline levels. Wolthuis et al. (126) injected radioactive iodinated serum albumin to determine the rate and severity of regional vascular pooling during LBNP. Pooling occurred in all dependent regions of the lower body, but rates and magnitudes were variable. These data demonstrate regional autoregulation, presumably for the purpose of protecting central blood volumes, in a similar fashion to the regional responses that occur during hemorrhage.

Differences in capacitance vessel density, compliance, and volume compositions in each area studied likely contributed to the nonuniform blood pooling. In this respect, application of LBNP induces cardiovascular responses that are different from hemorrhage. Clearly, reduction of blood volume would be expected to be greatest at the site of injury with hemorrhage and not dependent on vessel architecture or anatomic volume. Nevertheless, such reductions of volume, regardless of where they originate, will decrease venous return and activate similar compensatory mechanisms.

Neurohumoral Responses

Hemorrhage. Jacobsen et al. (60) recorded hemodynamic and hormonal responses to hemorrhage in anesthetized pigs during continuous bleeding to hypovolemic shock. A 10%

($\cong$275 ml) blood loss increased arterial pressure and heart rate; a 15% ($\cong$375 ml) blood loss decreased arterial pressure and heart rate (relative bradycardia) and increased epinephrine, norepinephrine, and pancreatic polypeptide; and an ~40% ($\cong$1,200 ml) blood loss further reduced arterial pressure and increased heart rate, epinephrine, norepinephrine, aldosterone, and pancreatic polypeptide. Sympathetic activation during hemorrhage is normal and necessary to maintain heart rate and peripheral vessel tone in both animals and humans. A 15% hemorrhage in rats dramatically increased both epinephrine and norepinephrine, along with neuropeptide Y (72). Adrenalectomy or chemical sympathectomy revealed that the majority of neuropeptide Y released in response to hemorrhage derives from sympathetic nerves and not the adrenal medulla (72). Neuropeptide Y works in concert with norepinephrine to facilitate vasoconstriction (119) and, therefore, likely plays an important role in maintaining arterial pressure during hemorrhage. Increased plasma catecholamine concentrations correlate directly to the severity of hemorrhage and arterial pressure reductions in bleeding dogs (18). In humans, nonhypotensive hemorrhage of ~5.5 ml/kg increases plasma norepinephrine levels and arterial pressure spectral power at the low frequency (51). Such responses indicate effective sympathetic compensation in the face of mild hypovolemia.

Reduction in heart size with central hypovolemia stimulates release of other vasoactive and volume regulatory hormones, such as arginine vasopressin and renin, although their role in maintenance of normal cardiovascular function during acute (compared with prolonged) hemorrhage in animals is probably minimal (36). Vasoactive hormonal responses to hemorrhage in animals may also be species dependent. For example, nonhypotensive hemorrhage does not appear to significantly affect release of arginine vasopressin in rabbits (85), but does in dogs (121). Hypotensive hemorrhage increases arginine vasopressin in the monkey (2), and plasma renin concentrations in the dog also increase during hemorrhage (14), but only at the point at which arterial pressures begin to decline precipitously. Thrasher et al. (112) confirmed that arterial baroreflexes control vasopressin but not renin release during graded hypotension in the dog.

As with nonhuman primates, increases in arginine vasopressin during hemorrhage in humans likely occurs at the point at which arterial pressures begin to decline, and increases are not simple linear functions of blood volume reductions (46). Arginine vasopressin does not change with removal of ~10% ($\cong$450–500 ml) of total blood volume. Similar results are observed for plasma renin (14, 46), but renin and vasopressin may increase abruptly with excessive blood loss. For example, circulating plasma renin was nine times normal in one bleeding patient studied before he was given 1,500 ml of blood (total amount of blood loss before infusion was not reported) when arterial pressure had decreased to 110/70 (14).

It is not surprising that vasopressin and renin do not seem to figure prominently in maintenance of normal cardiovascular function during acute hemorrhage. Humoral control may be considered to be a "second line of defense" to restore venous return in conjunction with the faster acting direct vasoactive influence of sympathetic nerves (89) and, as such, may be too slow to mount any effective defense against rapid blood loss. Release of vasoactive and volume-regulatory hormones before cardiovascular collapse may, however, contribute to restoration of arterial pressure after blood loss (95).

Sympathetic nerves supplying both veins and arterioles directly control peripheral resistance during hemorrhage, and activities of these nerves may be measured directly (18). Nonhypotensive hemorrhage increases sympathetic traffic in cats (28, 38) and dogs (7) but causes abrupt decreases after arterial pressures fall to a threshold level of ~30–40 mmHg (7, 28). Such abrupt reductions of sympathetic neural firings are not detectable in plasma hormonal samples before hemodynamic collapse, which provides strong rationale to measure sympathetic traffic directly.

LBNP. Similar to hemorrhage, nonhypotensive LBNP (up to 20 mmHg) has little effect on plasma renin, arginine vasopressin, aldosterone, or atrial natriuretic factor (31) in normal, healthy humans. Plasma renin activity increases moderately after prolonged (~20 min) LBNP exposure at 40 mmHg, but increased renin concentrations are not necessarily associated with increased vascular resistance (12). Moderate but significant increases in arterial and renal venous plasma renin and angiotensin II concentrations were observed at 18- and 27-mmHg LBNP (113). LBNP of 55 mmHg increased pancreatic polypeptide, epinephrine and norepeniphrine, and plasma renin activity (91). In another study, plasma renin activity did not increase significantly until ~50 mmHg during progressive LBNP (48). Arginine vasopressin does not seem to be affected by LBNP in subjects who tolerate negative pressure without showing signs of impending hemodynamic collapse (6, 25, 47, 77, 91) but increases significantly in susceptible subjects (6, 77). Mohanty et al. (69) showed that arginine vasopressin only increases in the presence of hypotension, and it is noteworthy that increases in arginine vasopressin occur in subjects experiencing nausea during LBNP exposure (77). [Nausea in and of itself can cause increases in arginine vasopressin (88).] Norsk et al. (78) confirmed that arterial baroreceptor unloading stimulates vasopressin release, but inhibition of arginine vasopressin does not further the development of hypotension during LBNP (57). This suggests that, although low-pulse pressure may signal release of vasopressin, vasopressin's role in arterial pressure regulation during central blood volume reduction in humans is minimal. However, other data suggest that vasopressin and renin may be useful markers for classification of subjects susceptible or not susceptible to cardiovascular collapse during LBNP. Convertino and Sather (26) found that subjects with low-LBNP tolerance increased their plasma vasopressin and renin concentration minimally, compared with high-LBNP-tolerant subjects who showed marked and significant increases in both vasopressin and renin. Convertino and Sather had carefully matched subjects for a number of different variables that other investigators did not control, which may explain why vasoactive hormones appear to play a predictive role in establishing susceptibility for cardiovascular collapse in this (26) but not other (6, 47, 77, 91) studies.

As might be expected, plasma catecholamines increase as a direct linear function of LBNP, up to at least 50 mmHg (48). However, as was the case with hemorrhage, interpretation of plasma concentrations of vasoactive substances seems to have little predictive value for abrupt cardiovascular collapse. With the advent of the microneurography technique in the late 1960s, it became possible to directly record sympathetic neural traffic destined for the vasculature supplying skeletal muscle in

humans (52) and, therefore, to more precisely document sympathetic responses to LBNP. Muscle sympathetic nerve activity (MSNA) increases during LBNP in response to central hypovolemia, mediated by both arterial and low-pressure cardiopulmonary baroreceptors (24, 108), and serves to increase peripheral vascular resistance to maintain constant arterial pressure.

Direct measures of MSNA could provide insight into cardiovascular responses to central hypovolemia that may predict susceptibility to impending cardiovascular collapse. Data from our laboratory (24, 27) and those of others (55, 93) have shown that increases in MSNA are well preserved during central hypovolemia induced by LBNP, up to the point of abrupt hypotension, at which time sympathetic traffic is withdrawn. Studies incorporating other hypotensive stimuli, including vasoactive drugs (96, 120), hemodialysis (19), and passive head-up tilting (15, 62, 70), have also documented sudden withdrawal of MSNA at the point of impending cardiovascular collapse.

Cardiovascular Collapse

Hemorrhage. As may be appreciated, ethical constraints limit the amount of data available describing human responses to hemorrhage. Some data are available from studies conducted in trauma emergency rooms, and some older studies provide insight into the effects of hemorrhage in humans in a controlled research environment. In a seminal study, Barcroft et al. (4) employed venesection and venous tourniquets (which trapped a portion of blood in the lower body) to induce cardiovascular collapse in which abrupt hypotension occurred in conjunction with bradycardia and reductions of total peripheral resistance. By 1944, Shenkin and coworkers (100) had categorized symptoms of hemorrhage in humans into three stages. Stage 1 refers to mild (~500 ml) hemorrhage, and subjects may have no symptoms while supine. On standing, pulse rates may rise, arterial pressures may fall, and subjects may feel weak. Stage 2 symptoms result from moderate (up to ~1,000 ml) hemorrhage and include relative bradycardia and symptoms of impending cardiovascular collapse on standing. Stage 3 describes symptoms of severe hemorrhage (>1,000 ml) in which subjects may experience symptoms of collapse while still supine. On standing, both arterial pressures and pulse rates fall suddenly in conjunction with nausea, dizziness, and pallor, and subjects experience frank cardiovascular collapse (100).

Cardiovascular collapse occurs in a majority of human subjects after removal of ~1,000 ml of blood (68, 84, 100), but removal of as little as 500 ml of blood may also cause collapse (123). Collapse is characterized by a sudden drop in arterial pressure (4, 68, 100) mediated by reductions of peripheral resistance (4, 123), presumably through reflex vasodilation of arterioles (4). Relative bradycardia was observed in 9 of 12 subjects after removal of ~1,000 ml of blood (100), and 4 of these 9 experienced symptoms of impending hemodynamic collapse. In general, these studies suggest that the likelihood of progression to stage 2 hemorrhage and cardiovascular collapse is $\cong$50% when blood loss ranges from 1,000 to 1,500 ml ($\cong$20–25% total blood volume).

LBNP. An early study by Epstein et al. (35) outlined the progression to cardiovascular collapse with LBNP by classifying responses into two phases, similar to the two stages leading to hemorrhagic shock outlined several years earlier by Shenkin et al. (100). With this construct, arterial pressures are sustained by appropriate sympathoexcitation to maintain vascular resistance up to the point at which this compensation apparently fails. Symptoms of impending cardiovascular collapse occur in conjunction with sympathetic withdrawal, loss of peripheral vessel tone, and relative bradycardia.

Sympathetic withdrawal before symptoms of impending hemodynamic collapse is suggested by a lack of increase in plasma catecholamine concentrations during progressive LBNP in one subject who experienced a vasovagal episode (48). In another, vasovagal symptoms occurred in conjunction with dramatic reductions of renal norepinephrine overflow and dramatic increases of plasma angiotensin II and renin concentrations (113). Although it has been suggested that subjects susceptible to cardiovascular collapse respond to central blood volume reductions with blunted adrenergic responses (43, 124), plasma catecholamine concentrations evaluated to make these conclusions were drawn after subjects presented with presyncopal symptoms. It seems as likely that subjects have normal or even enhanced sympathetic responses followed by abrupt sympathetic withdrawal at the onset of symptoms (27). Evans et al. (36) found that subjects susceptible to collapse increased their plasma catecholamine concentrations more during LBNP than their nonsusceptible counterparts before peripheral resistance fell. Our laboratory documented enhanced sympathetic nerve responses in subjects who developed symptoms of impending collapse compared with nonsusceptible subjects (24). These data (24, 27), and data of others (36), suggest that there exists a threshold of sympathetic activation above which continual stimuli serve to decrease rather than increase neural traffic with persistent reductions of central blood volume. It has been proposed that acute hypovolemia during LBNP or hemorrhage stimulates ventricular mechanoreceptors, which may override arterial baroreceptors, resulting in sympathetic withdrawal and cardiovascular collapse (116).

Figure 5 shows MSNA during baseline supine rest with 0-mmHg chamber pressure and during −60-mmHg decompression. This subject displayed appropriate sympathetic baroreflex activation and inhibition with falling and rising pressures and tolerated 12 min of LBNP without incident. Figure 6 shows this same subject (*top*) and a different subject (*bottom*) who had apparently reached a threshold for sympathetic activation such that arterial pressure could no longer be maintained. In the subject who experienced symptoms of impending cardiovascular collapse (*bottom*), abrupt sympathetic withdrawal occurred in conjunction with hypotension and other symptoms, including nausea and tunnel vision.

Sympathetic Neural Responses

Sympathetic activation during hemorrhage and LBNP is fundamental to the maintenance of arterial pressure and cardiac filling, and sympathetic withdrawal is associated with hypotension and progression to cardiovascular collapse [equivalent to stage 2 hemorrhage (95)]. In this regard, Rea and coworkers (87) provided good evidence that LBNP is an effective model to study sympathetic responses to hemorrhage in humans. MSNA was recorded in subjects during nonhypotensive LBNP at 0, 5, 10, and 15 mmHg and before and after removal of 450 ml of blood. As shown in Fig. 7, a 450-ml hemorrhage decreased central venous pressure from a control value of $\cong$6

Fig. 5. Representative arterial pressure and muscle sympathetic nerve activity (MSNA) during baseline supine (*top*) and −60-mmHg LBNP (*bottom*). a.u., Arbitrary units. (Data are from unpublished observations of V. A. Convertino and W. H. Cooke.)
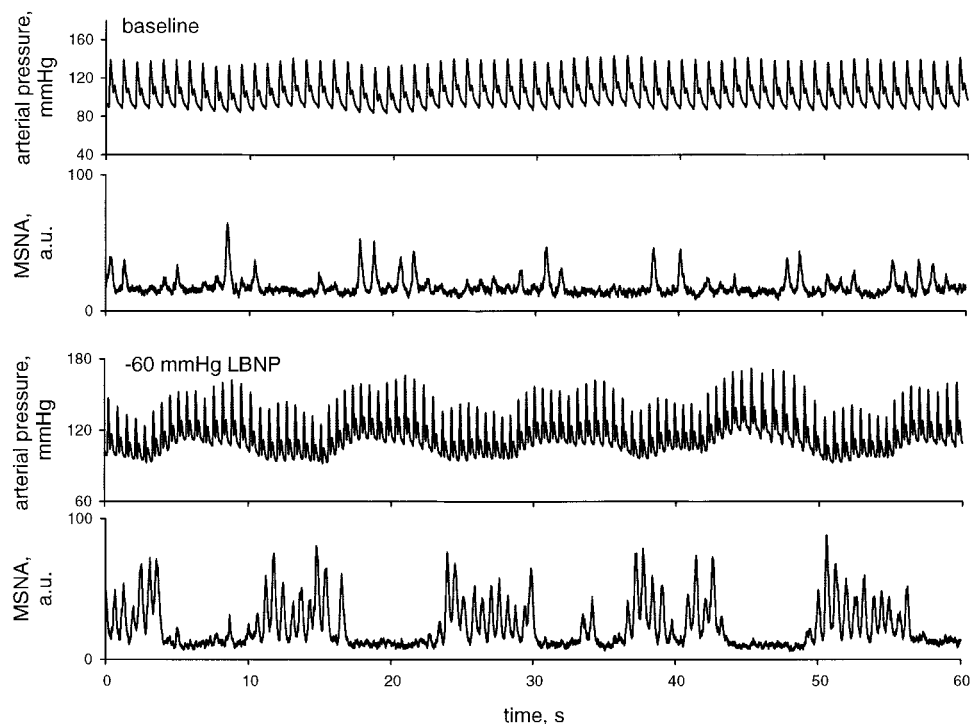
to 3.8 mmHg. Corresponding MSNA increased from a control value of ≅300 to 380 U/min. If these responses to hemorrhage are compared with those during LBNP, it can be surmised from similar magnitudes of MSNA increases that LBNP on the order of roughly 10 mmHg corresponds to ~450 ml of blood loss. This value is consistent with other studies (54, 110). Because Rea et al. (87) only studied MSNA responses to a single blood draw, it is impossible to confirm that MSNA responses to hemorrhage are linear, but MSNA does seem to respond linearly to progressive LBNP (24, 27). Importantly, because MSNA responses to nonhypotensive hemorrhage and LBNP are similar, Rea et al. (87) concluded that intra-abdominal pressure receptors thought to be activated with LBNP do not play a major role in sympathetic activation during central hypovolemia. Because of this, low-level nonhypotensive LBNP shows promise as a noninvasive model to predict human sympathetic responses to nonhypotensive hemorrhage.

Maintaining adequate nerve recordings during higher levels of negative pressure (i.e., above about −30-mmHg chamber pressure) is difficult because even small movements of the

Fig. 6. Arterial pressure and MSNA are shown for a subject who tolerated −60-mmHg LBNP (*top*; nonsusceptible to cardiovascular collapse) and a subject who experienced symptoms of cardiovascular collapse during −60-mmHg LBNP (*bottom*). [Data reproduced from Cooke and Convertino (27).]
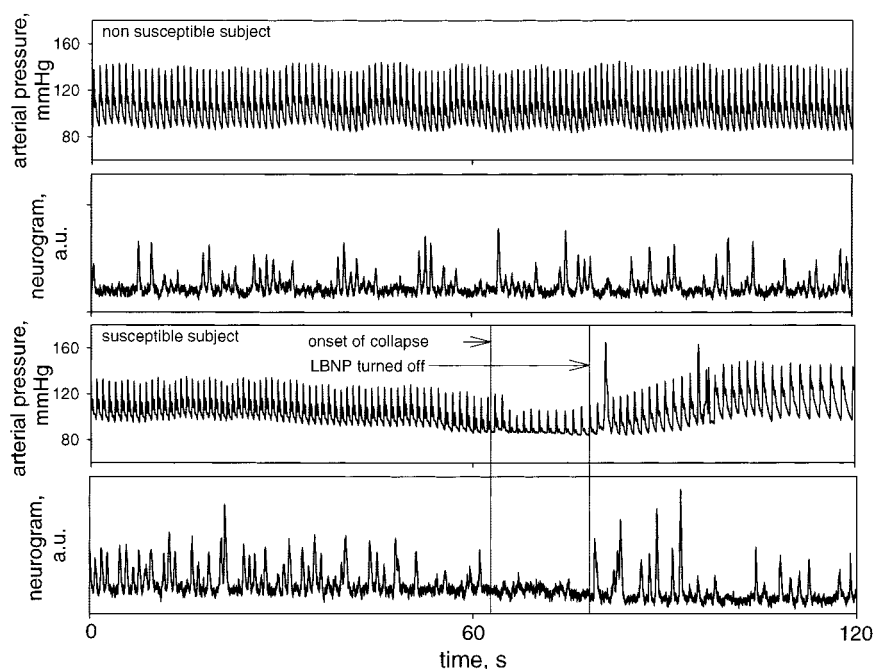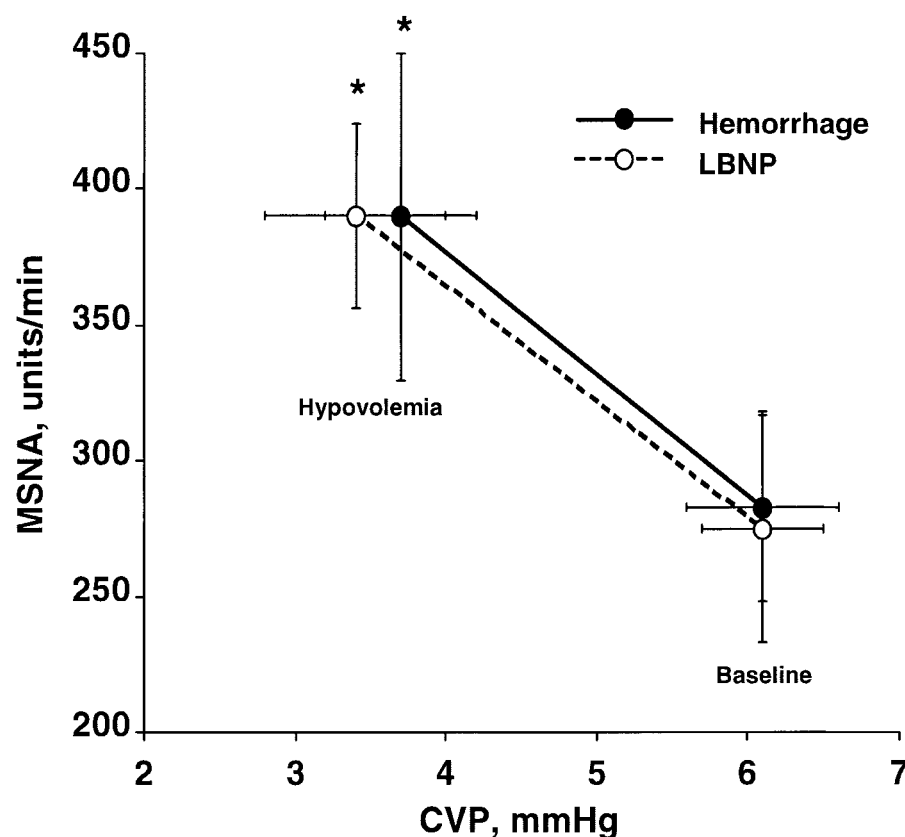
Fig. 7. Comparison of relationships between central venous pressure (CVP) and MSNA during -10-mmHg LBNP ($\circ$, dashed line) and 450-ml hemorrhage ($\bullet$, solid line) in 9 human subjects. Circles and lines represent mean $\pm$ SE values. *$P < 0.05$ compared with baseline. [Data modified from Rea et al. (87).]

microelectrode may cause the signal to be lost or otherwise rendered unanalyzable. In a recent study, adequate nerve recordings were maintained in several subjects during LBNP exceeding 30 mmHg (24). Figure 8 shows tight linear relationships between MSNA increases and stroke volume (Fig. 8A) and cardiac output (Fig. 8B) decreases up to -60-mmHg chamber pressure ($n = 4$ at -60 mmHg). Two of the four subjects depicted in Fig. 8 eventually experienced symptoms of impending cardiovascular collapse in conjunction with abrupt sympathetic neural withdrawal. Although it is unclear whether sympathetic responses to high-level (i.e., potentially hypotensive) LBNP are similar to hypotensive hemorrhage, withdrawal of MSNA at the point of cardiovascular collapse agrees with early observations of hemorrhagic shock in humans. At the onset of circulatory collapse, arterial pressures fell (4, 68) secondary to sudden drops of peripheral resistance (4, 123). In these early studies, it is reasonable to propose that peripheral resistance fell due to sympathetic neural withdrawal.

CONCLUSIONS

The concept that LBNP may be an effective model to study cardiovascular responses to acute hemorrhage in humans is tenable from several perspectives. However, it should be emphasized that application of LBNP does not mimic all of the responses observed in traumatic hemorrhage, as LBNP clearly does not induce tissue trauma or subsequent metabolic responses (e.g., acidosis). Rather, data suggest that LBNP may be used as a model to study acute hemodynamic responses to the central hypovolemia associated with hemorrhage. In this respect, responses to both LBNP and hemorrhage can be classified into phases where arterial pressures either are maintained or are not maintained primarily through sympathoexcitation. Based on linear relationships between either hemorrhage or LBNP and central venous pressure or stroke volume, it appears that moderate LBNP on the order of 10–20 mmHg is equivalent to blood loss of $\sim$400–550 ml. Data outlining relationships between more severe hemorrhage and levels of LBNP are less clear, but suggest that LBNP between 20 and 40 mmHg corresponds to blood loss of between 500 and 1,000 ml, and LBNP of 40–60 mmHg corresponds to >1,000-ml blood loss (see Table 1).

A summary of physiological response comparisons taken from work discussed in the preceding sections is shown in Table 2. (Table 2 is valuable as a general summary, as experimental designs, data collection methods, and techniques varied among experiments.) Heart rate progressively increases with hemorrhage or LBNP until shock or cardiovascular collapse. Collapse is associated with relative bradycardia at high-level LBNP and during hemorrhagic shock, although $\sim$60–70% of severely bleeding patients respond with tachycardia. Arterial pressures are either maintained or slightly increased with progressive reductions of stroke volume, cardiac output, and central venous pressure, until the onset of shock or collapse associated with abrupt hypotension. Under both conditions of hemorrhage and LBNP, sympathetic neural activation is fundamental to the maintenance of arterial pressure, and either blunted or exaggerated sympathetic activation occurs before shock or collapse. However, evidence suggests that, in all subjects, onset of hypotension occurs in conjunction with

sympathetic neural withdrawal. Also shown in Table 2 are differential vasoactive and volume regulatory hormonal responses at various stages of hemorrhage and levels of LBNP. Due to local autoregulation of various vascular beds, evaluation of catecholamines and other vasoactive hormones from plasma samples provides little insight (beyond global responses) into progression to cardiovascular collapse. The summary data presented in Table 2 show that, in all cases except heart rate (where tachycardia is associated with a high-mortality rate), physiological responses to hemorrhage and LBNP are similar, suggesting that LBNP may be a useful model to simulate acute hemorrhage in humans. The significance of future studies using LBNP to simulate the central hypovolemia of hemorrhage will be dependent on successful development of algorithms possessing higher discriminant value than pulse and blood pressure in determining degrees of hemorrhage across a broad patient population. Such algorithms might then be applied clinically to identify bleeding victims who will likely progress to hemorrhagic shock and require life-saving intervention(s).

Fig. 8. *A*: relationship between relative change (%∆) in stroke volume and MSNA during progressive central hypovolemia induced by graded levels of LBNP. Values are means ± SE (*n* = 6 for the 3 highest stroke volumes; *n* = 4 for the 2 lowest stroke volumes). [Data reproduced from Convertino and Cooke (24).] *B*: relationship between %∆ in cardiac output and MSNA during progressive central hypovolemia induced by graded levels of LBNP. Values are mean ± SE (*n* = 6 for the 3 highest stroke volumes; *n* = 4 for the 2 lowest stroke volumes). (Data are from unpublished observations of W. H. Cooke and V. A. Convertino.)

Table 2. *Comparison of global physiological responses to hemorrhage and LBNP*

Classification	Stage I		Stage II		Stage II		Stage III	
Hemorrhage	**Mild**		**Moderate**		**Severe**		**Shock**	
LBNP	10–20 mmHg		20–40 mmHg		>40 mmHg		Collapse	
Variable								
HR	**↑**	↔	**↑**	↑	**↑**	↑	**↑**	↓ ↓
MAP	**↔**	↔	**↑**	↔	**↑**	↑	**↓**	↓ ↓
SV	**↓**	↓	**↓**	↓	**↓**	↓	**↓**	↓ ↓
Q̇c	**↓**	↓	**↓**	↓	**↓**	↓	**↓**	↓ ↓
CVP	**↓**	↓	**↓**	↓	**↓**	↓	**↓**	↔ ↓↔
SNA	**↑**	↑	**↑**	↑	**↑**	↑	**↓**	↓
NE	**↑**	↑	**↑**	↑	**↑**	↑↔*		
PVR	**↑**	↑	**↑**	↑	**↑**	↑	**↓**	
AVP	**↔**	↔	**↔**	↔	**↔**	↔↑*	**NA**	↑
PR	**↔**	↔	**↔**	↔	**↔**	↔↑*	**NA**	↑
ANG II	**NA**	↔	**NA**	↔	**NA**	↑	**NA**	↑
PPH	**↔**	↔	**↔**	↔	**↑**	↑	**↑**	↑

Under each condition, variables either increase (↑), decrease (↓), do not change (↔), or show differential responses (↓↔; ↔↑). Responses to hemorrhage are shown in bold font, and responses to LBNP are shown in regular font. NA, data not available or too limited to present; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; Q̇c, cardiac output; CVP, central venous pressure; SNA, sympathetic nerve activity; NE, norepinephrine; PVR, peripheral vascular resistance; AVP, arginine vasopressin; PR, plasma renin; ANG II, angiotensin II; PPH, pancreatic polypeptide hormone. *Directional changes only in subjects susceptible to hemodynamic collapse or at the onset of hypotension.

Future Research

Battlefield performance. Soldiers are well conditioned, and highly conditioned athletes have been shown to possess decreased ability to regulate arterial pressure during LBNP (86, 105). However, it has not been determined whether mechanisms underlying blunted autonomic responses to central hypovolemia in athletes are due to exercise training or to some other characteristic associated with high aerobic capacities (20, 63). Furthermore, physical exertion, psychological (emotional) stress, and limited opportunity for adequate food and water intake are common features in the battlefield environment. Such stressors place unique demands on physiological regulatory systems that could compromise normally adequate compensatory responses to a hemorrhagic combat injury and subsequently lead to unexpected complications during trauma care. Soldiers become dehydrated, and reduction of total circulating blood volume negatively impacts performance (64). The effects of dehydration combined with simulated hemorrhage with progressive LBNP have not been studied from a combat or trauma perspective. In addition, relations among physiological consequences of psychological stressors associated with battle, in combination with hypovolemia, could impact progression to hemorrhagic shock. Mental stress increases sympathetic traffic (1), and epinephrine released during stressful situations in conjunction with norepinephrine as a cotransmitter could activate the Bezold-Jarish reflex or otherwise affect sympathetic responsiveness [the "epinephrine hypothesis" (37, 102)], resulting in earlier onset of cardiovascular collapse during hemorrhage. The effects of exogenous epinephrine administration in hypovolemic subjects during simulated hemorrhage with LBNP are unknown.

Simulating rates of blood loss. LBNP has at least one other benefit as a model to study hemorrhage that has not yet been
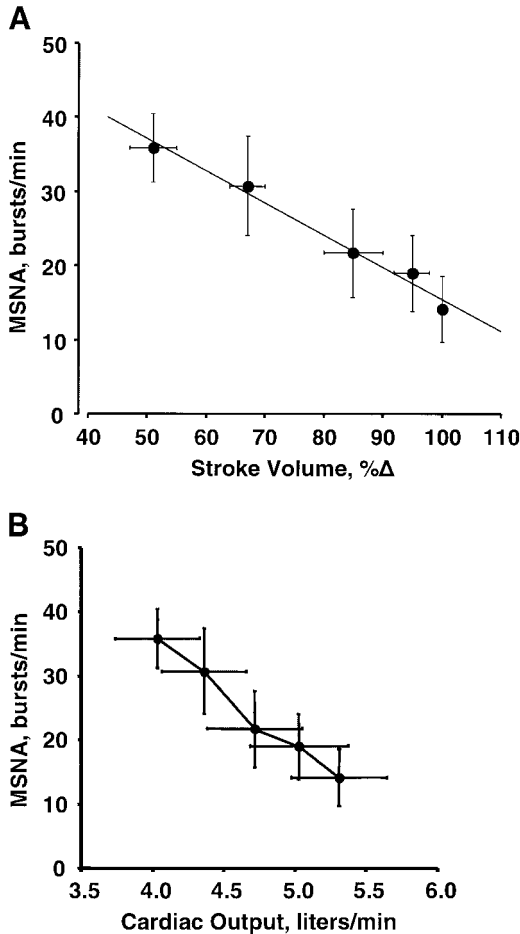
explored, and that is the ability to manipulate the speed of decompression. Understanding physiological responses to hemorrhage may depend importantly on the speed at which blood is lost. Patients losing blood are able to withstand larger total volume reductions when bleeding is slow, compared with when it is fast. Physiological compensation for slow bleeding, including redistribution of blood to the central circulation through sympathoexcitation, better maintains arterial pressure, cardiac output, and central blood volume compared with abrupt responses to the direct physiological effects of rapid bleeding (5). In this regard, LBNP may be an effective tool to study the impact of fast vs. slow bleeding by manipulating the rate of chamber decompression.

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